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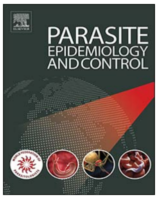

Parasitic and zoonotic meningoencephalitis in humans and equids: Current knowledge and the role of *Halicephalobus gingivalis*

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ABSTRACT

Halicephalobus gingivalis is a saprophytic nematode parasite that causes a rare form of fatal meningoencephalomyelitis in equids, humans, and ruminants. This nematode has neurotropic activity, but has also been found in the kidney, liver, lungs, optic nerves and even heart of its host. Despite the zoonotic potential and severity of the disease, the epidemiology, pathogenesis, life cycle, and risk factors are poorly understood. Cases have been reported from several countries in Europe countries and North America but none is recorded in Africa except Egypt. This review looks at the historical overview, morphology, diagnosis, treatment and summary of reported cases in humans and equids. We recommend the parasitic helminthic infection in the differential list of meningoencephalitis involving humans and animals worldwide despite its rareness.

1. Introduction

Nematodes (round worms) are among the most diverse taxa in the animal kingdom with over 26,000 species described (Hugot et al., 2001). Nematodes are the most abundant soil metazoans (Bernard, 1992). Parasitic species may infect either animal (vertebrates and invertebrates) or man. Despite their diversity in terms of lifestyles, nematodes share a general common anatomy and physiology.

Halicephalobiasis is a helminthic infection caused by *Halicephalobus gingivalis*. The latter is a free-living soil saprophytic nematode known to cause opportunistic infections in the form of fatal meningoencephalomyelitis mainly in equines. *Halicephalobus gingivalis*, also known as *Micronema deletrix*; *Halicephalobus deletrix* belongs to the nematode Order *Rhabditida*, Family Paragrolaimidae. Currently, there are eight described species of *Halicephalobus*, and only *H. gingivalis* has been reported to infect humans and equines - predominantly in horses (Anderson et al., 1998) and to a lesser extent zebras (*Equus grevyi*) (Isaza et al., 2000) and donkeys (Schmitz and Chaffin, 2004). Recently, *H. gingivalis* has been reported to cause bovine meningoencephalomyelitis in ruminants (calves), where parasites were identified morphologically and diagnosis confirmed by molecular analysis of the large subunit (LSU) and small subunit (SSU) rRNA genes of the parasite (Enemark et al., 2016). Other species within the genus *Halicephalobus* include *H. limuli*; *H. similigaster*; *H. minutum*; *H. parvum*; *H. palmaris*; *H. intermedia* and *H. laticauda* (Anderson et al., 1998).

The organism is commonly referred to by its generic name, because the species are difficult to distinguish morphologically (Ondrejka et al., 2010) although, the shape of the tail and descriptions of the reproductive tract seem to distinguish *H. gingivalis* from other species in the genus. Only parasitic female adults, larvae and eggs have been isolated from parasitized hosts, confirming that *H.*

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gingivalis can reproduce parthenogenetically, although how *H. gingivalis* infects human and equine hosts is still largely speculative (Papadi et al., 2013). In the environment, *H. gingivalis* has been isolated from horse manure and compost (Steel et al., 2010).

Human infections are very rare, but all cases described to date involved fatal meningoencephalitis (Lim et al., 2015) and of the reported equine cases only four horses have survived (Dunn et al., 1993; Pearce et al., 2001; Schmitz and Chaffin, 2004; Muller et al., 2008). The success of this parasite in causing its pathology may be unconnected to its mode of reproduction. Current reports have demonstrated the presence of this parasite in localities where it was presumed to be absent. This review aims to provide more light on this silent but potentially zoonotic parasite causing fatal meningoencephalitis in humans and equids around the world and the need to develop a diagnostic tool to diagnose the infection antemortem as majority of the diagnosis has been at postmortem.

2. Parasite biology

2.1. Historical perspective

Stefanski (1954) was the first to accurately describe the nematode. He found the worms in a granuloma in the gingivae of a horse in Poland. He first placed the species in the genus *Rhabditis*. It was later transferred to the genus *Tricephalobus* by Dougherty (1955). Sudhaus (1976) placed *gingivalis* in *Trilabiatus*. Later, Andrassy (1952) placed the species in *Halicephalobus* where it remains till date. Anderson and Bemrick (1965) described *Micronema deletrix* from a nasal tumour of a horse in Minnesota, USA. The clinical pathology of this case was later described by Johnson and Johnson (1966) who reported the nematodes mainly in large granulomas in the maxillae. Andrassy (1952) and Geraert et al. (1988) in reviews of the genus *Halicephalobus* apparently regarded *H. deletrix* as a possible synonym of *H. gingivalis*. Although they gave no reasons for this possibility it can probably be assumed that it was because *H. gingivalis* and *H. deletrix* were both from lesions in horses.

2.2. Morphology

The typical morphologic features of *Halicephalobus deletrix* are the distinctive rhabditiform esophagus with corpus, isthmus, and bulb and their reproductive tracts are didelphic with dorsiflexed ovaries at the posterior end. Only female worms are found in tissue. Adult female worms are 250 to 460 μm by 15 to 25 μm. The larvae stages are smaller and have the same features as the fully developed worms but lack a reproductive system. The larvae are 250 to 300 μm long and 15 to 20 μm wide, with a rhabditoid esophagus (70 to 90 μm long). Eggs are oval, elongated, thin-shelled and colorless 40 to 55 μm by 20 to 25 μm in size (Lim et al., 2015). This nematode characteristically lacks lateral or cuticular alae. The cuticle of the worm is thin and has fine striations (Gardiner et al., 2000).

2.3. Life cycle

The life cycle of *Halicephalobus* sp. is poorly understood. But it is believed that the adult female worm reproduce asexually by parthenogenesis. Asexual reproduction is usually considered as an evolutionary dead end, and difficulties for asexual lineages to adapt to a fluctuating environment are anticipated due to the lack of sufficient genetic plasticity (Castagnone-Sereno and Danchin, 2014). This mode of reproduction is common among nematodes of the order Tylenchida and Rhabditida. When a female reproduces using parthenogenesis, she has no need for a male. This means that a parthenogenetic female can spend more time and energy seeking food and shelter while such resources are readily available. Without the need for males, parthenogens can reproduce faster than species that reproduce sexually. In fact, a group of parthenogenetic females can produce a certain number of offspring with only half as many parents as a similarly sized group of sexually reproducing animals. Surprisingly, only the females - usually found in association with eggs and immature larvae - have been identified and characterized from tissue samples till date (Lim et al., 2015).

2.4. Phylogenetics of Halicephalobus gingivalis

A recent study carried out by Pintore et al. (2017) revealed that the *H. gingivalis* isolates belonged to Lineage 3, which includes other isolates from Japan and USA. Only a few sequences are available on public databases, with little information on date of sample collection and location. However, the sequence similarity data and phylogenetic analysis confirm that there is no correlation between location and genetics in *H. gingivalis* based on 28S rRNA gene data. Furthermore, there was no apparent correlation between lineages and clinical manifestation of *H. gingivalis*, although the number of available sequences is limited (Nadler et al., 2003). Notably, the only two *H. gingivalis* sequences available from human cases are those recently reported in Australia and Germany (Lim et al., 2015; Monoranu et al., 2015). Both were classified by phylogenetic analysis as belonging to Lineage 1. Sequencing of more isolates and the analysis of multiple loci will help in establishing a correlation between phylogenetic clustering, geographic correlation, clinical signs and the zoonotic potential of *H. gingivalis*. Genetic variation study was used to distinguish the *H. gingivalis* isolated from Danish calves to published isolates by comparing the large subunit (LSU) rRNA and the small subunit (SSU) rRNA genes of *H. gingivalis*, which was found to have a genetic variation of 0.5% - 4.4% and 0.7–8.6%, respectively (Enemark et al., 2016).